~~Example of~~ Research Proposal for the Mice Breakout Group

Use of chemically induced oxidative DNA damage in human risk assessment

Biomarkers offer the possibility of using human data to make health risk assessments more meaningful, realistic, and cost effective (Fowle and Sexton, 1992). Understanding the human health risk associated with occupational chemical exposures involves defining the events between an exposure and the resulting disease. In this process, biomarkers provide a measure of the internal dose, the biologically effective dose, and early biological effects that are predictive of disease (Hattis and Silver, 1993; Schulte, 1993; Perera et al., 1991). Therefore, biomarkers have the potential to lead to an improvement in the ability to detect and accurately measure human-dose response relationships (Hattis and Silver, 1993). To achieve this, the relationship between the biomarker and the disease must be known if biomarkers are to be relevant to regulatory decisions (La and Swenberg, 1996). While many biomarkers have shown promise in cross-sectional and case-control studies in demonstrating a link between exposure and the biomarker, these research results, for the most part, have yet to be effectively translated into risk assessments and preventive health policies (Perera, 2000).

Chemically induced oxidative stress in generally considered an adverse health effect. This has lead to an increased interest in oxidative DNA adducts such as 8-hydroxydeoxy-guanosine (8-OHdG), which are produced by a variety of chemicals that generate free radicals during metabolism (Kasai, 1997). 8-OHdG DNA adducts are linked to specific mutations as well as chemically induced cancer in experimental animals (Fiala et al ., 1989; Kuchino et al., 1987). Additionally, numerous cross-sectional epidemiological studies such as those with tobacco smoke or benzene have attempted to link oxidative DNA damage with these environmental or occupational exposures (Toraason, 1999). Despite the established link between these exposures and oxidative DNA, and the link between these exposures and the disease outcomes, little or no attempt has been made to determine the disease risk that is associated with increased oxidative DNA damage. As a consequence, there is considerable uncertainty in the utility of oxidative DNA adducts for prediction of disease outcome. Therefore, there is a need to assess the use of oxidative DNA damage as a biomarker and determine if its measurement has application to human risk assessment.

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